

## REMARKS

### ***Overview***

In the Office Action under reply, claims 22-31 and 39-41 were examined, claims 1-21 and 32-38 having been canceled previously. The claims stand rejected as follows:

(1) claims 22-30 and 40-41 are rejected under 35 U.S.C. §103(a) as unpatentable over Soon-Shiong et al., US 5,560,933 ("Soon-Shiong");

(2) claims 31 and 39 are rejected under 35 U.S.C. §103(a) as unpatentable over Soon-Shiong in view of Russell et al., *Bone Marrow Transplantation* (1999) 24, pp. 1177-1183 ("Russell") and further in view of Vook et al., US 2003/0129233 ("Vook").

The rejections are overcome in part by the amendments made herein, and are otherwise traversed for at least the reasons set forth below.

### ***Claim amendments***

With the amendments made herein, claim 22 is amended to recite that the buoyancy agent may be a combination of a gas and an oil. Support for this amendment may be found, *inter alia*, on page 4 (lines 1-3) and on page 29 (line 30 et seq.) of the original specification. No new matter is added by this amendment.

Claim 25 has been amended to include antibiotics and combinations of agents in the list of therapeutic agents. This amendment is supported, *inter alia*, on page 16, lines 17, 18, and 23 of the original specification. No new matter is added by this amendment.

New claims 42-52 have been added. Examples of supporting disclosure for these new claims are as follows. Claims 42-46 are supported by claims 5-9 as originally filed. Claim 47 is supported by claim 10 as originally filed as well as by page 2, lines 1-6 of the original specification. Claim 48 is supported by claim 33 as originally filed, as well as by page 16, line 17 et seq. of the original specification. Claim 49 is supported by page 4 (lines 1-3) and on page 29 (line 30 et seq.) of the original specification. Claim 50 is supported by page 18, lines 3 and 10 of the original specification. Claims 51 and 52 are supported by the original specification at page 18, line 11, and page 30, line 13. No new matter is added by these claims.

***Rejection under 35 U.S.C. §103(a)***

Claims 22-30 and 40-41 are rejected under 35 U.S.C. §103(a) as unpatentable over Soon-Shiong. The rejection is traversed.

A rejection under 35 U.S.C. § 103 requires the following analysis: "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved" *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Then, "the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a *prima facie* case of obviousness) is more probable than not" (MPEP § 2142). The Action fails to meet this standard. As shown by the arguments set forth below, the preponderance of the evidence suggests that Soon-Shiong does not provide a *prima facie* case of obviousness.

The instant claims are directed to a method for intrathecally administering a composition to the central nervous system of a subject, wherein the composition comprises a plurality of biodegradable polymer particles having a therapeutic agent and a buoyancy agent contained therein, and wherein the composition is controllably buoyant within the cerebrospinal fluid to allow targeted delivery of the therapeutic agent within the central nervous system. Such a method is not disclosed in Soon-Shiong.

Soon-Shiong is directed to *in vivo* delivery of substantially water insoluble active agents in which the active agent is delivered in a soluble form or in the form of suspended particles (Soon-Shiong, Abstract). The Action states that "[i]t would have been *prima facie* obvious at the time of the Applicants' invention to utilize the invented particles to administer an active pharmaceutical agent intrathecally, because Soon-Shiong explicitly teaches that the invented compositions are suitable for the *in vivo* administration of active substances and defines *in vivo* delivery to include intrathecal administration" (Action at 5-6). In fact, as described below, the invention described in Soon-Shiong is significantly different from the instant invention in a number of ways. Such differences are so significant that the skilled artisan would not have found the instant claims obvious in view of the disclosure of Soon-Shiong.

## 1. Differences between Soon-Shiong and the instant claims

Soon-Shiong discloses delivery of water insoluble drugs, and mentions intrathecal delivery in a laundry list of applications that are described as suitable. The primary technical aspects of the methods of Soon-Shiong focus on *suspending* or *dissolving* water insoluble drugs during the *manufacturing* process. The Action acknowledges that "Soon-Shiong does not explicitly teach the inclusion of a buoyancy agents" (Action at 6). Applicants agree, and for at least the reasons set forth below, further emphasize that the use of a buoyancy agent as described in the instant claims would not have been obvious to the skilled artisan in light of Soon-Shiong.

Furthermore, the claims describe a composition for intrathecal delivery that provides targeted delivery of a therapeutic agent in the central nervous system (CNS). Not only does Soon-Shiong fail to mention targeted delivery in the CNS, but for the reasons described below, the compositions of Soon-Shiong would not be suitable for providing such targeted delivery.

## 2. Unsuitability of the particles of Soon-Shiong

For a variety of reasons, the materials of Soon-Shiong would not be suitable for controlled, targeted delivery to the central nervous system as claimed in the invention.

First, Soon-Shiong specifically formulates particles to contain a polymeric shell and a pharmaceutically active agent within the shell. Upon degradation of the polymeric shell, the particles disintegrate and the active agent is released in vivo. The active agent is completely contained within the polymeric shell, and the active agent may be in the form of a solid (i.e., one or more solid particles) or a liquid (e.g., dissolved in a solution). *See, e.g.*, Soon-Shiong, col. 4, lines 14-28. A suspending or dissolving agent such as vegetable oil may be present, for example, in the interface between the active agent and the polymeric shell, or in the solution containing the active agent that is surrounded by the polymeric shell. *See, e.g.*, Soon-Shiong, col. 6, line 47 to col. 7, line 50.

If such a composition were to be delivered to the cerebrospinal fluid, active agent would be released only after the polymeric shell bioerodes. However, after the polymeric shell bioerodes, the active agent would be released into the CSF either as a solid mass or as a liquid in solution. In the case of solid particles, the particles of active agent would move about in the CSF according to the density of the active agent. Alternatively, in the case of liquids, the liquid active agent would either disperse in the CSF (if soluble) or coalesce into a separate liquid phase of active agent (if insoluble). In either case, the buoyancy of the active agent would be completely

uncontrolled once the polymer shell bioerodes. Targeted delivery within the CSF would therefore be impossible using the particles disclosed in Soon-Shiong. Thus, based on the disclosure of Soon-Shiong, the skilled artisan would not consider using vegetable oil as a buoyancy agent as disclosed in the instant application. In other words, the disclosure of Soon-Shiong does not provide a method for providing controllably buoyant particles for delivery of pharmaceutical agents in the cerebrospinal fluid, as required by the pending claims.

Second, Soon-Shiong uses vegetable oil during the *manufacturing* process in order to ease the manufacturing of compositions with non-soluble drugs. In contrast, the instant invention uses agents such as vegetable oil in order to affect the behaviour of pharmaceutical formulations *in vivo*. Soon-Shiong uses suspending agents to address an issue of manufacturability of compositions, but does not mention any modification of the use of such agents. Again, the use of vegetable oil in the manner presently claimed would not be obvious to the skilled artisan based on the disclosure of Soon-Shiong.

Third, substantial modifications would be necessary in order for the materials of Soon-Shiong to be capable of carrying out the instantly claimed methods. Incorporation of vegetable oil as a buoyancy agent (rather than a suspension or dissolution agent) would require, for example, modification of the location of the oil in the formulations. Suspension of insoluble agents, as reported in Soon-Shiong, requires that the oil be localized between the active agent and the polymer shell. This arrangement, however, does not allow the active agent to be carried to the desired position within the CNS according to the buoyancy of the oil. Soon-Shiong does not suggest modifying this arrangement in any way that would result in a composition that could target delivery of the therapeutic agent within the CNS.

It should be noted that the term "suspend" (as in "suspended particles") as used in Soon-Shiong is not related to buoyancy-type suspension. The skilled artisan would understand that Soon-Shiong is referring only to chemically suspending (i.e., dispersing an insoluble material within a non-solvent, such as fat globules present in milk) pharmaceutical agents. In contrast, the meaning of the term "suspend" that is relevant to the instant invention refers to the *spatial* location of particles within the CNS. For example, the particles of the invention may be suspended in the upper regions of the CNS. Although certain materials such as vegetable oils are suitable for both types of suspension, disclosure of one type does not necessarily render the other type obvious. This is particularly true in the instant case, since other aspects of the particles of Soon-Shiong render such particles unsuitable for preparing controllably buoyant compositions

(as described above).

### 3. Improper use of hindsight

Soon-Shiong suggests using vegetable oils and other compounds as suspending or dissolving agents. The dispositive issue is whether the skilled artisan, after reading Soon-Shiong, would consider using such compounds as a buoyancy agent to create a composition that is suitable for intrathecal delivery and is controllably buoyant in the cerebrospinal fluid. Of course, upon reading applicants' disclosure it is apparent that such oils can be used in this fashion. However, *without* the aid of applicants' disclosure, the skilled artisan would not find it obvious to prepare formulations for intrathecal delivery using buoyancy agents as claimed.

Vegetable oil has a number of physical properties, including boiling point, viscosity, density, freezing point, flash point, color, conductivity, polarity, molecular weight, etc. The use of vegetable oils as a buoyancy agent focuses on one of these properties (i.e., density). There is no particular reason, however, for the skilled artisan to modify the use of vegetable oil described in Soon-Shiong based on the density of vegetable oil rather than basing such modification on any of the other physical properties of vegetable oil. This is particularly true since Soon-Shiong does not suggest that the suspending/dissolving components described therein could have other uses. In particular, Soon-Shiong does not suggest that such components could be used as buoyancy agents or in any way other than as suspending/dissolving agents. Without such guidance, the skilled artisan would have no reason to choose the particular modifications to the materials of Soon-Shiong that would be required in order to arrive at the invention of the instant claims. In other words, modifying Soon-Shiong to arrive at the instant claims requires more than simply applying information that is commonly known in the field. "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007)). The conclusion that the vegetable oil of Soon-Shiong can be used in buoyancy-controlled compositions for intrathecal delivery improperly relies on hindsight and applicants' disclosure.

### 4. Conclusion

In summary, the technology described in Soon-Shiong was not meant to provide a formulation that is controllably buoyant within the CNS. Even though one of the components in the formulations of Soon-Shiong (i.e., vegetable oils, disclosed in Soon-Shiong as a

dispersing/dissolution agent) is suitable for use as a buoyancy agent in the current invention, Soon-Shiong neither suggests such a use nor provides any disclosure that would cause the skilled artisan to modify the formulations of Soon-Shiong in such a way as to arrive at the instant claims. Indeed, the modifications that would be required to provide a formulation capable of providing targeted delivery of a therapeutic agent in the CNS are significant and non-obvious. Accordingly, Soon-Shiong does not support a *prima facie* case of obviousness of the instant claims, and applicants respectfully request withdrawal of the rejection.

***Rejection under 35 U.S.C. §103(a)***


Claims 31 and 39 are rejected under 35 U.S.C. §103(a) as unpatentable over Soon-Shiong in view of Russell and further in view of Vook. This rejection is traversed.

The shortcomings of the teachings of Soon-Shiong are discussed above with reference to the rejection of claims 22-30 and 40-41. In summary, Soon-Shiong does not teach the use of buoyancy agents in a formulation that is suitable for targeted delivery of an active agent in the CNS. Neither Russell nor Vook overcome this deficiency of Soon-Shiong, as neither reference discloses the use of buoyancy agents in delivery of therapeutic agents to the CNS. Accordingly, the combination of Soon-Shiong with Russell and Vook fail to provide a *prima facie* case of obviousness for claim 22 and claims depending from claim 22 (i.e., claims 31 and 39). Applicants respectfully request withdrawal of the rejection.

**CONCLUSION**

Applicants submit that the claims of the application are in condition for allowance. Applicants respectfully request withdrawal of the rejections, and prompt issuance of a notice of allowance. If the Examiner has any questions concerning this communication, or would like to discuss the application, the art, or other pertinent matters, a telephone call to the undersigned would be welcomed.

Respectfully submitted,

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